The rising incidence of Rheumatic Fever in Maori & Pacific Children: Can it be Stopped?

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Te Whare Wānanga o Otāgo
Health Sciences

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Outline

- Key features of RF
- RF epidemiology
- Opportunities to intervene in causal pathway
  - Improving determinants
  - Improving specific risk/protective factors
  - Probiotic (BLIS) to reduce GAS pharyngitis
  - Screening & treating GAS pharyngitis
  - GAS vaccination
- Conclusion

Rheumatic heart disease

Impetigo

Strep throat

Streptococcus pyogenes =Group A Streptococcus (GAS)

~20% are asymptomatic carriers

Gram positive cocci completely sensitive to penicillin

Rheumatic fever

Streptococcal toxic shock

Cellulitis and necrotizing fasciitis

Scarlet fever

Key features of RF

Diseases following GAS:

- **Superficial infection**
  - **Pharyngitis**
  - **Impetigo, Pyoderma**
- **Invasive diseases**
  - **Septicaemia**
  - **Pneumonia, osteomyelitis…**
  - **Necrotising fasciitis**
- **Toxin mediated diseases**
  - **Scarlet fever**
  - **Streptococcal toxic shock syndrome**
- **Post-streptococcal autoimmune sequelae**
  - **Acute rheumatic fever / rheumatic heart disease**
  - **Post-streptococcal glomerulonephritis**

Key features of RF

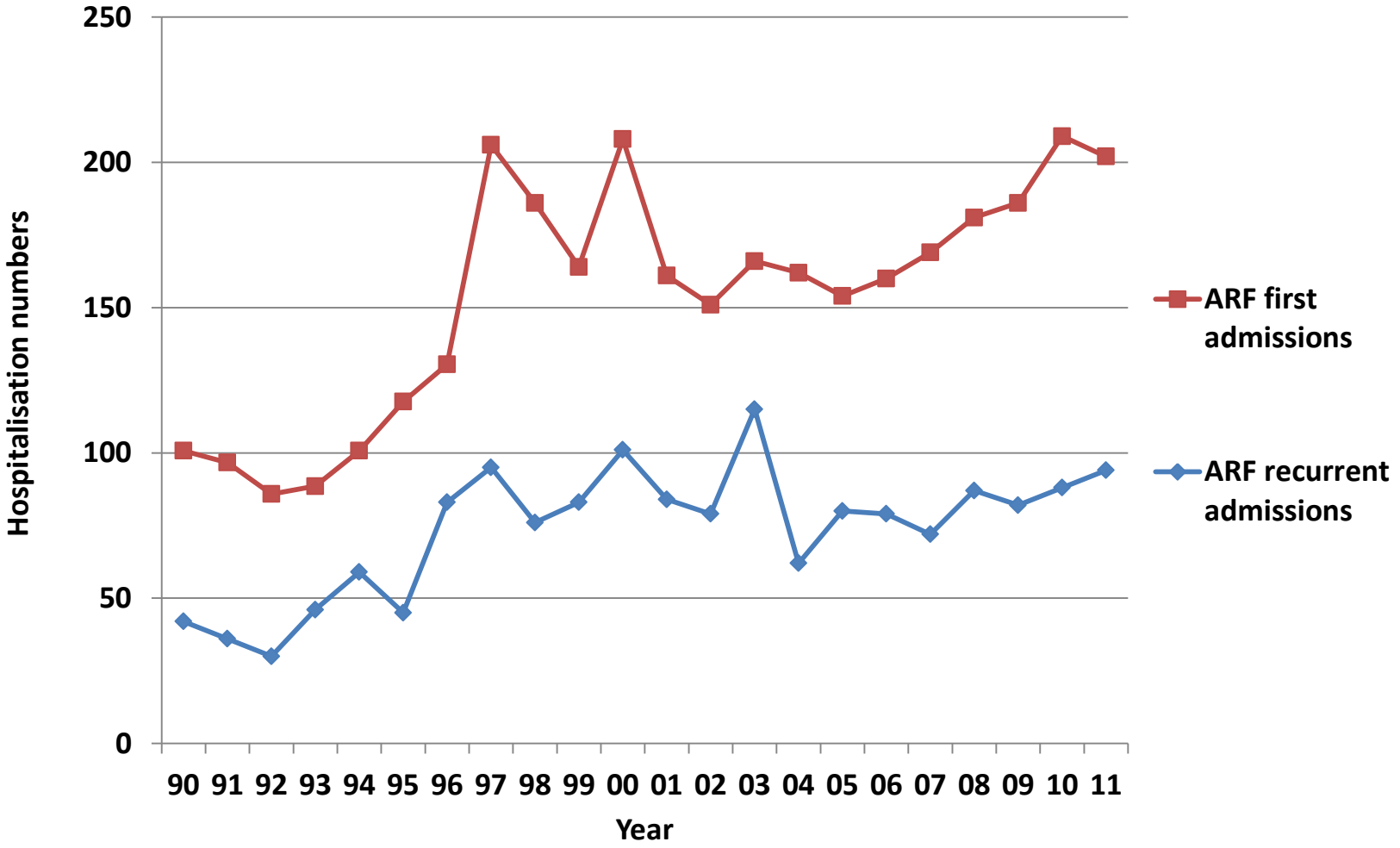
- **RF is a complex 3-stage disease:**
  - **GAS infection - throat (pharyngitis) and possibly skin (impetigo), may be asymptomatic**
  - **Acute rheumatic fever (ARF) – immune-mediated, may be asymptomatic**
  - **Rheumatic Heart Disease (RHD) – chronic disease, possibly requiring several ARF episodes**
- **RF may be difficult to diagnose**
  - **2-6 weeks after a sore throat**
  - **Painful swelling of joint(s)**
  - **Fever, Tiredness, stomach ache (mesenteric adenitis)**
  - **Sometimes a rash or lumps under the skin (immune depositions)**
  - **Fidgety, unusual movements (chorea)**
  - **Evidence of heart murmurs signals RHD**

Key Features of RF

- **Largely confined to children aged 4 to 19 years (median age 9 years)**
- **In NZ, now almost exclusively a disease of Maori & Pacific children**
- **Additional association with deprivation**
- **Now virtually absent in developed countries**
- **NZ ~180 cases a year (4.5/100,000)**
  - **43/100,000 in Maori children**
  - **73/100,000 in Pacific Island children**
- **Australian Aboriginals ~600/100,000**
- **Fiji Prevalence of RHD in 5-15 age group = 840/100,000**

RF Epidemiology

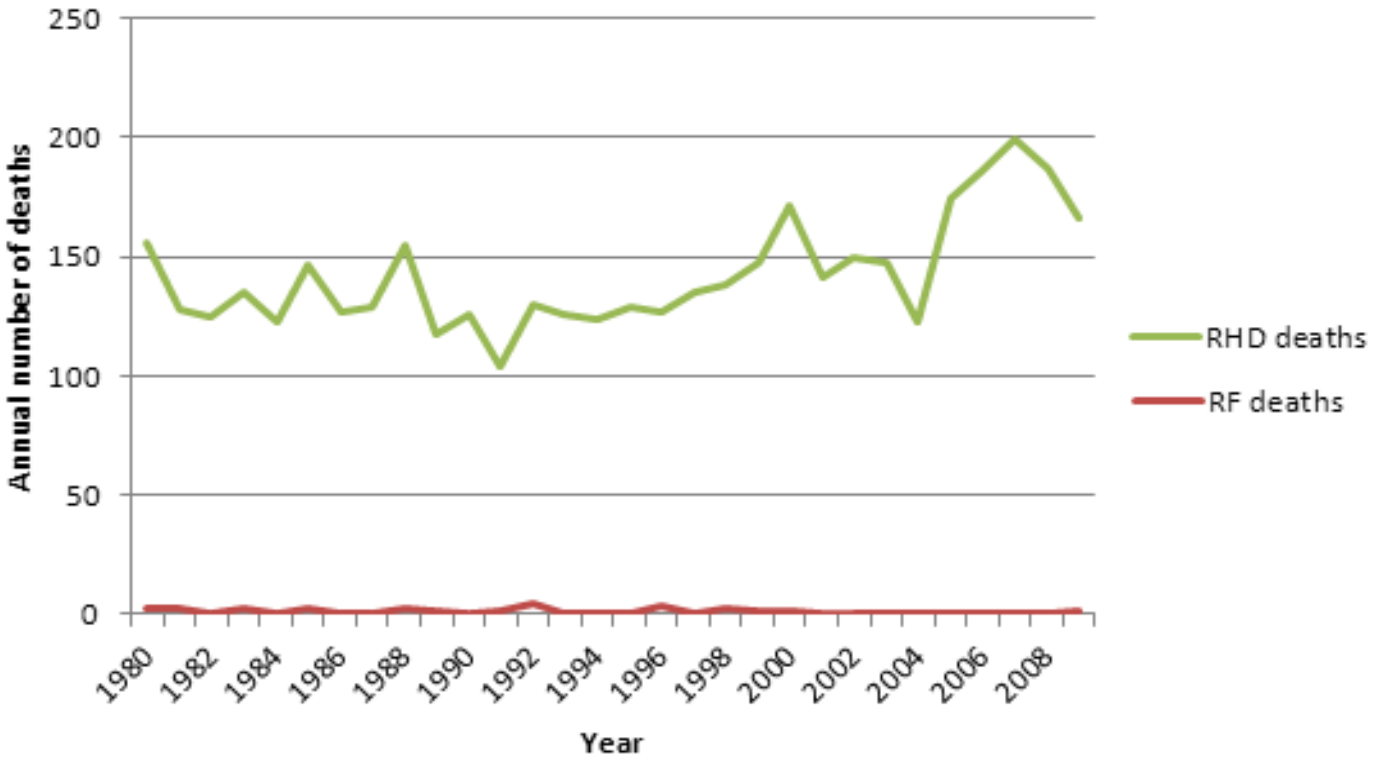
Increasing incidence ARF



Source: Ministry of Health, NMDS hospitalisation data.

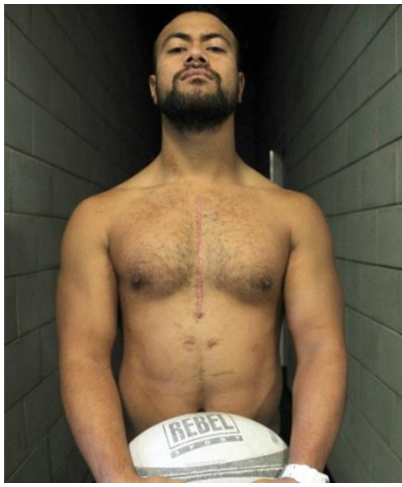
RF Epidemiology

High mortality from RHD



RF is one of NZ's biggest infectious disease killers (140 RHD deaths per year)

Source: Ministry of Health, NMDS mortality data



Buxton Popoali'I, former Highlanders rugby player, shows his scars from mitral valve replacement operation needed after he developed RHD

RF Epidemiology

Increasing ethnic inequalities

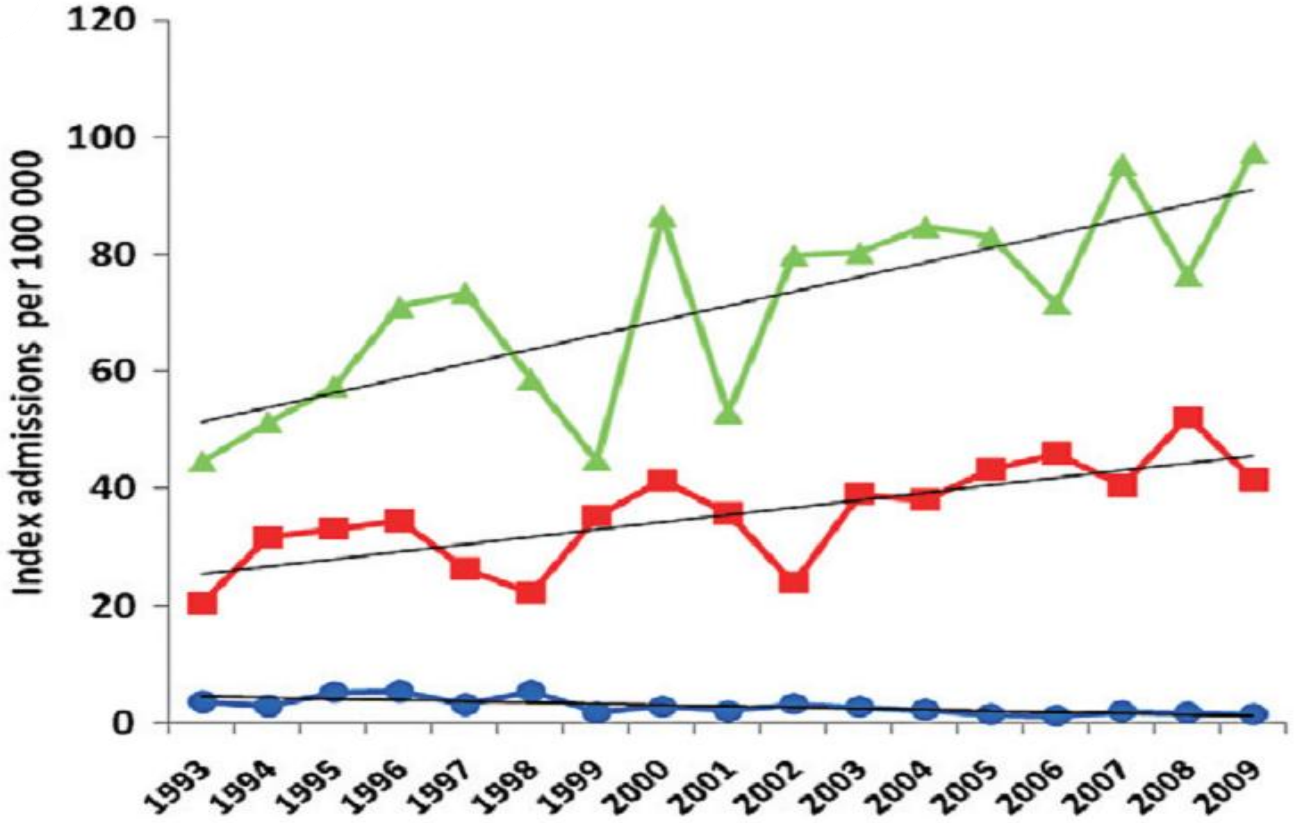


Fig. 1 Annual index cases and incidence rates for acute rheumatic fever in 1993–2009 for children 5 to 14 years of age. Māori (—■—); Pacific (—▲—); non-Māori/Pacific (—●—).

Rate Ratios
European/
Other=Ref

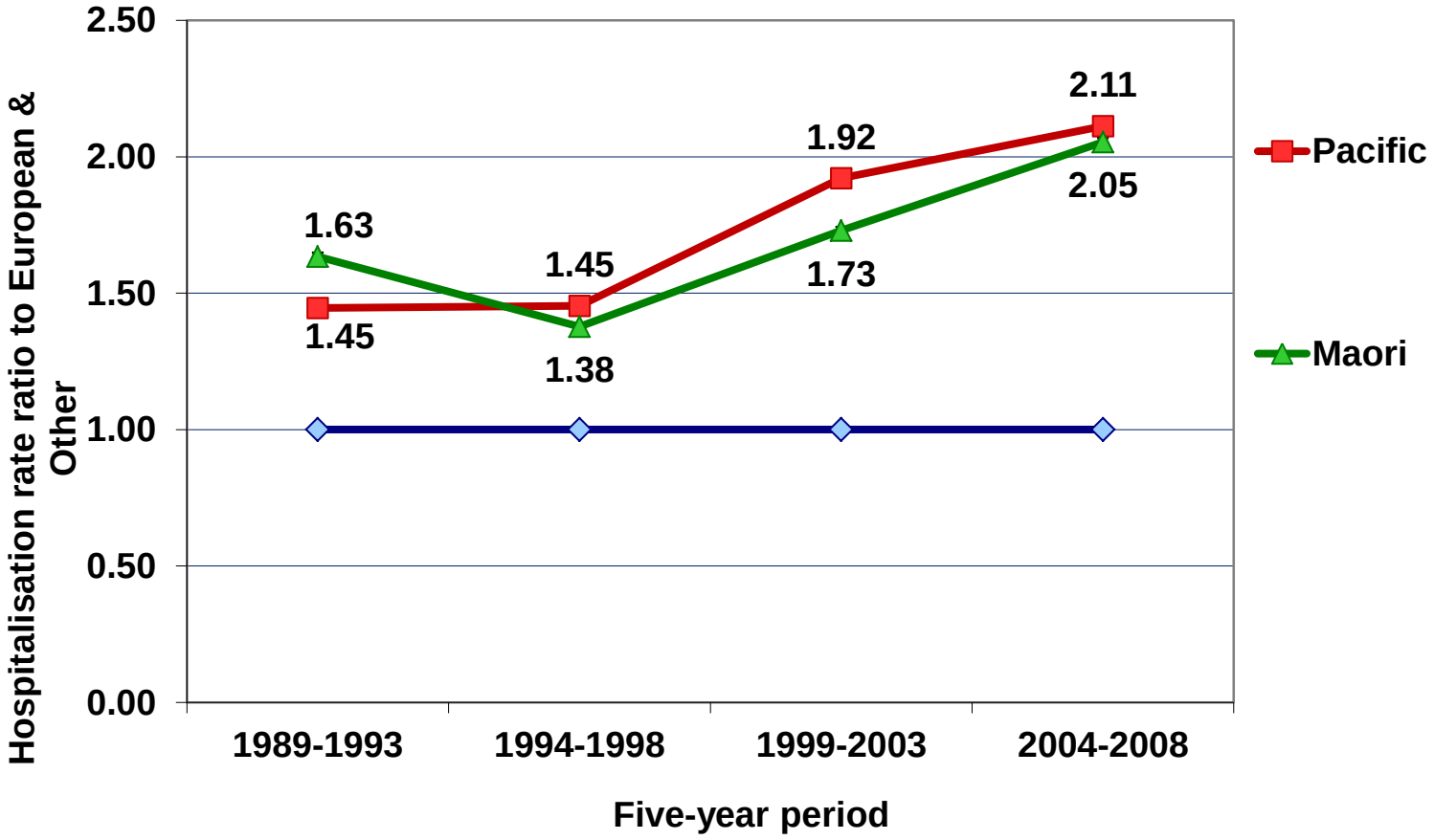
1993
Maori = 6
Pacific = 12

2009
Rate Ratio
Maori = 36
Pacific = 72

Source: Milne, Lennon, et al. J Paed Child Health 2012; 48: 685-91

RF Epidemiology

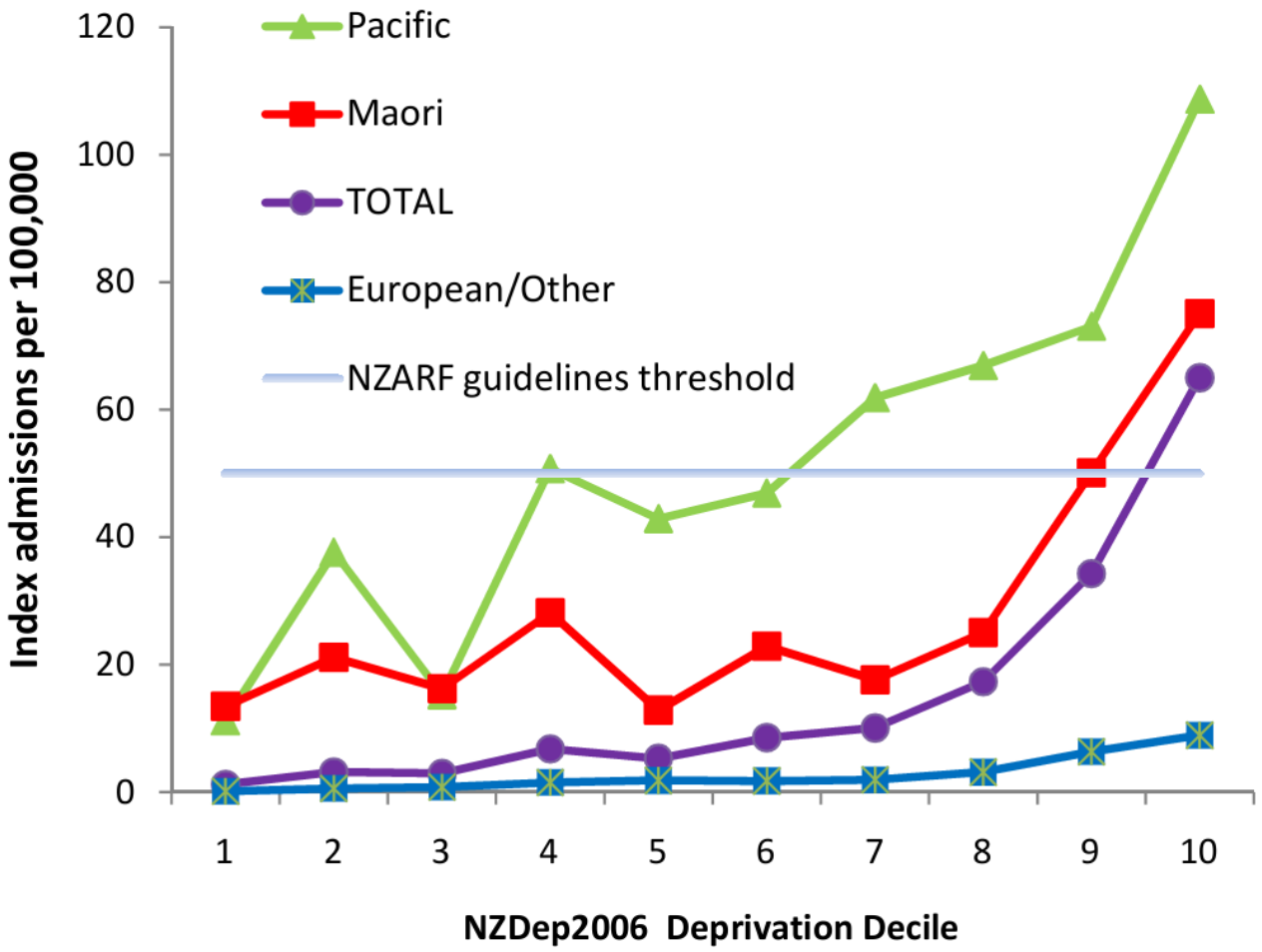
Comparison with ethnic inequalities for total IDs, Children < 5 years, Ratio of Māori & Pacific ID rates to European/Other, 1989-2008



Source: Baker et al. Lancet 2012; 379, 1112 - 19

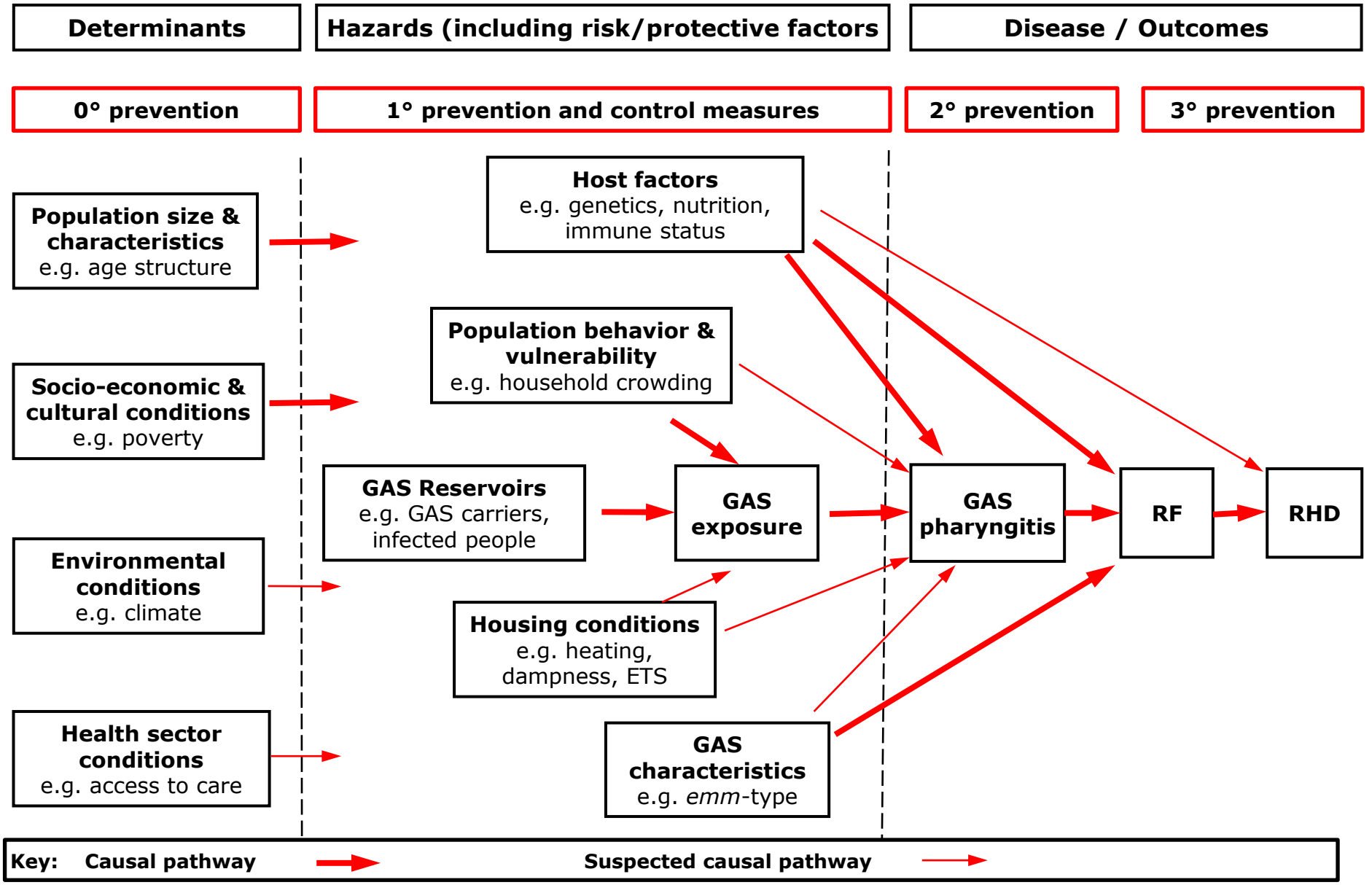
RF Epidemiology

Average annual RF rate for children 5-14, by NZDep & ethnicity, 2000-09



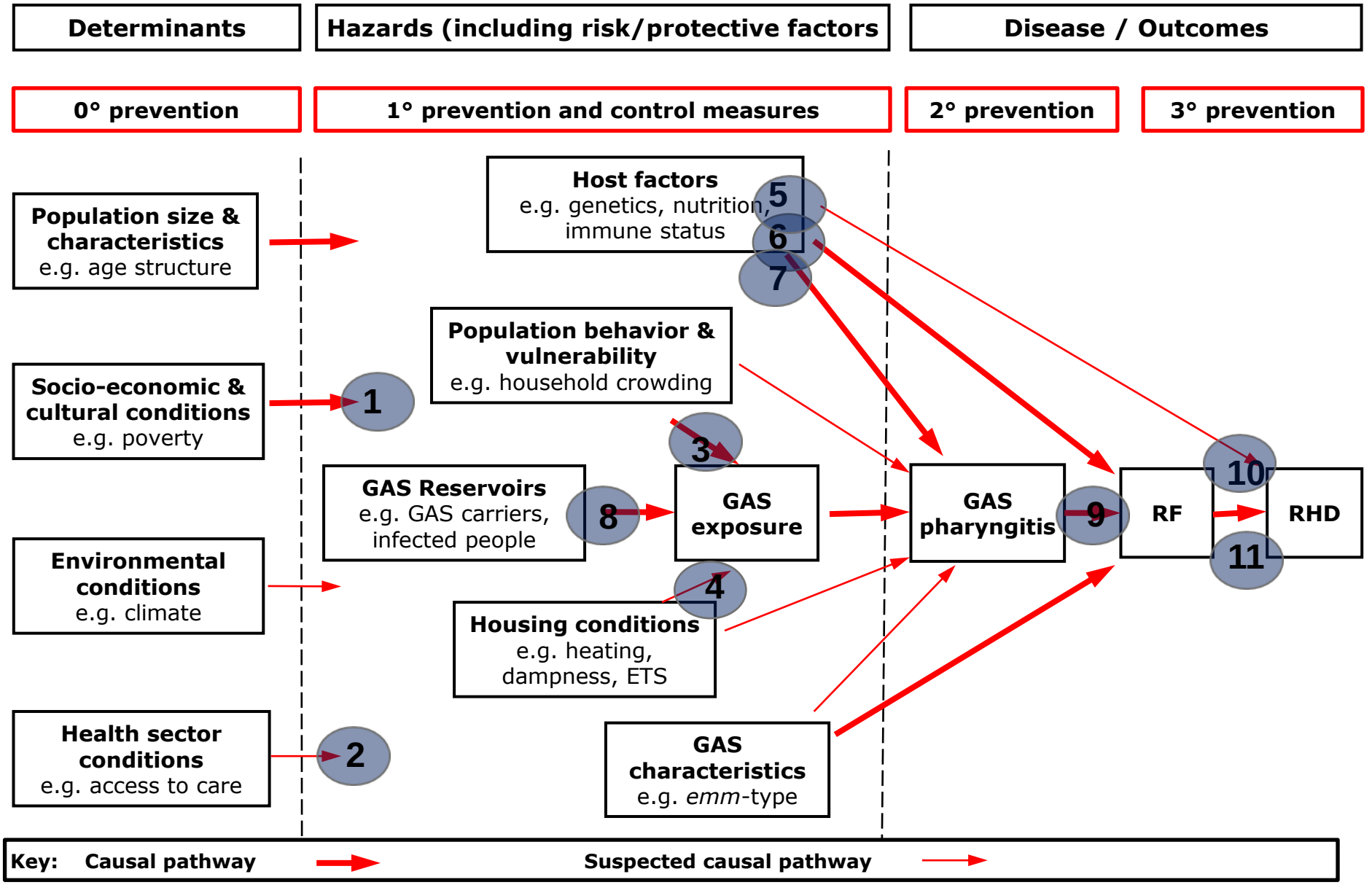
Source: Milne, Lennon, et al. Report to MoH, 2009

Causal pathway & Intervention Points



Source: Oliver, Pierce, Baker. BMC Pub Health 2012; 379, 1112 - 19

Causal pathway & Intervention points



Source: Oliver, Pierce, Baker. BMC Pub Health 2012; 379, 1112 - 19

Causal pathway & Intervention points

Altering ARF Determinants

1. **Poverty reduction**
2. **Improved healthcare, health literacy, housing**

Primary prevention of ARF

3. **Reduced household crowding (structural, functional)**
4. **Improved indoor housing env. (warm, dry, no ETS)**
5. **Improved nutrition**
6. **GAS vaccination**
7. **Probiotics to reduce GAS carriage/pharyngitis**
8. **Screening & treating household contacts of cases**
9. **Screening & treating GAS pharyngitis**

Secondary prevention of ARF

10. **Antibiotic prophylaxis of ARF cases**
11. **Echocardiography screening to detect RHD**

RF Prevention Programme (RFPP)

- **Government target to reduce the incidence of RF by two thirds, to 1.4 cases per 100,000by 2017**
- **>$65 million of extra Budget funding**
- **Sore throat management through free school and community clinics – school based programme now covering ~50,000 children**
- **DHBs contracted for healthy housing referral service**
- **Awareness raising for high risk communities.**

Intervention research

Potential intervention	Research
Improving determinants (income, education, healthcare, housing)	'National' case-control study of RF risk factors
Improving specific risk/protective factors (functional crowding, micronutrients)	'National' case-control study of RF risk factors
Probiotic (BLIS) to reduce GAS carriage/pharyngitis	Randomised controlled trial (RCT) of BLIS
Screening & treating GAS pharyngitis (school-based, primary care)	Analysis of throat swabbing laboratory data & linked ARF case data
GAS vaccination	Vaccine candidate selection & ultimately clinical trial

RF risk factors research

Risk factors for RF:

• **Age**	**+++**
• **Ethnicity**	**++**
• **Poverty**	**+**
• **Access to health services**	**+**
• **Household crowding**	**+/?**
• **Household dampness**	**+/?**
• **Urbanisation**	**?**
• **Poor nutrition**	**?**

Sources:

- ***Steer, Carapetis, et al. Paediatr. Child Health 2002; 38: 229–34***
- ***Kerdemelidis, Lennon, et al. J Paediatr. Child Health 2010; 46 534–48***
- ***NZ Guidelines Group, RapidE: Rheumatic Fever, 2011***
- ***Baker, McDonald, et al. Household crowding & risk of IDs, 2012***

RF risk factors research

Best quality studies show no significant association between household crowding and risk RF or RHD

Study, year	Country Time period	Study design	Out-come measure	Exposure measure: crowding	Comparison group	Subjects	No. subject	OR / RR, 95%CI	p-value
Kurahara 2006	US 1998-2001	Case-control	RF	No. in subjects bedroom	Hospital controls with non-RF heart conditions	<18yo	26 cases + 41 controls	Mean cases: 1.4; controls: 1.7	NS
Vlajinac, 1991	Yugo-slavia 1982	Case-control	RF	>2 persons / room	Neighbour-hood & school controls	<18yo	148 cases + 444 controls	OR=1.60, CI 0.61-3.00	NS
Oli, 1999	Ethiopia 1995	Cross - section	RHD preval-ence	Persons / bedroom (2+ in univariate analysis)	Children without RHD	10-15yo	9378	OR=1.01, CI 0.99-1.02	NS
Coggon, 1993	UK 1936-1989	Cohort (retro)	Mortality from RHD	Crowding index 1.00+ vs. <0.50	No RHD as adults	All ages	8138	-	NS

Source: Baker, McDonald et al. 2012. Household crowding & risk of IDs: A systematic literature review & meta-analysis of observational studies.

RF risk factors research

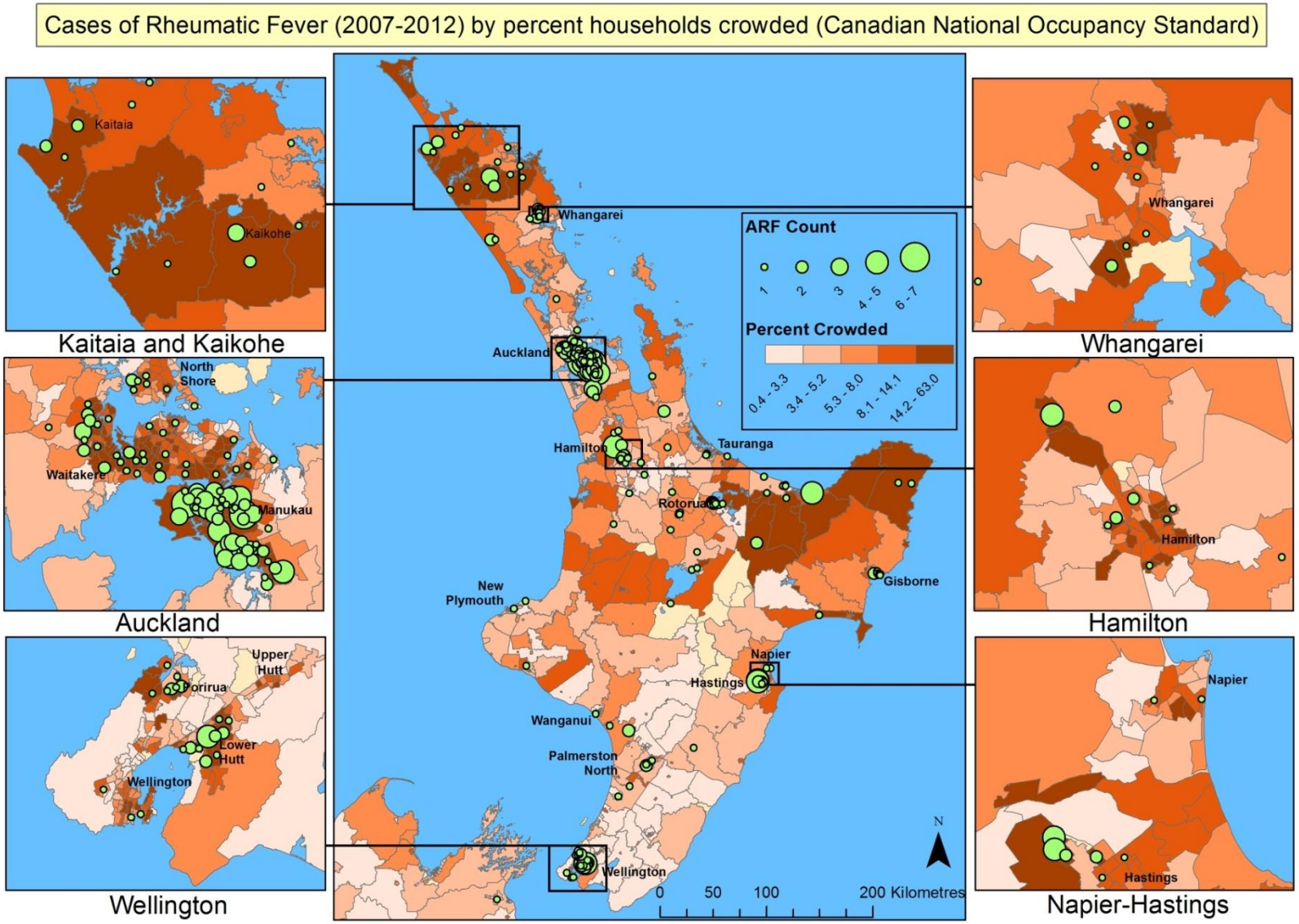
Classical studies in US Air Force Base barracks in 1950s.

Acquisition of streptococcal infections increased when beds moved closer together ⇒ Biological basis for effect of crowding on ARF incidence

Barracks, Warren Air force Base

Source: Wannamaker LW. The epidemiology of streptococcal infections. In: McCarty M, ed. Streptococcal Infections. Columbia University Press, New York, 1954

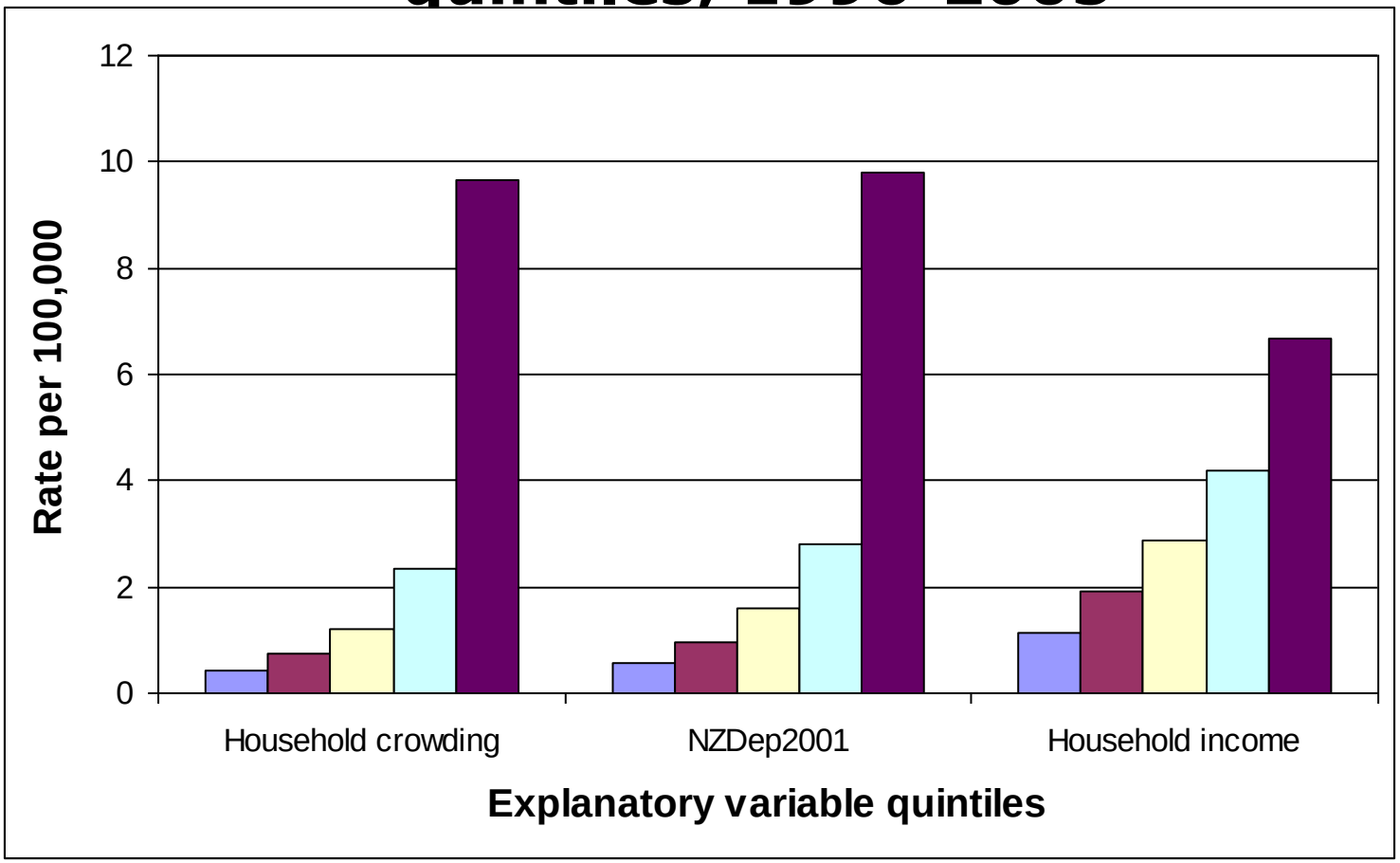
RF risk factors research



Source: NZ Ministry of Health, 2012.

RF risk factors research

Average annual RF first admission rates by household crowding, deprivation, income quintiles, 1996-2005



Source: Jaine, Baker, Venugopal. Paed Infect Dis J 2011; 30: 315-9

RF risk factors research

Multivariate analysis

- Risk of ARF hospitalisation in relation to CAU features
- Zero inflated negative binomial regression
- **Restricted to Māori & Pacific 5-14 years**, 1996-2005

Explanatory variable	Incidence rate ratio	95% conf. interval	p-value
Household crowding	1.022	1.010-1.034	0.000
Household income	1.006	0.998-1.024	0.523
Prop. 5-14 year olds	1.038	1.005-1.071	0.022

Source: Jaine, Baker, Venugopal. Paed Infect Dis, 2011; 30: 315-9

RF risk factors research

National case-control study aims

1. Identify potentially modifiable environmental risk factors for RF, (e.g. household crowding).
2. Identify potentially modifiable host factors for RF, such as vitamin D deficiency and anaemia.
3. Establish whether current or recent skin infection is associated with an increased risk of RF.
4. Establish whether access to healthcare, including pharyngitis treatment, is protective for RF.
5. Establish whether poor oral health is associated with an increased risk of RF.
6. Establish whether specific group A streptococcus (GAS) organisms are associated with RF.
7. Contribute to identifying immunological factors associated with an increased risk of RF.
8. Establish whether certain genetic factors (the HLA-DRB1 locus) are associated with RF.

RF risk factors research

National case-control study methods

- **Design: Case-control study**
- **Location: 'National' (Northern half of North Island includes ~80% ARF cases)**
- **Time period: 2 years, from 1 Sept 2014**
- **Cases = 200 ARF cases meeting NZ case definition (confirmed, probable)**
- **Controls = 2 groups**
  - **Matched controls – 400 (tightly matched by age group, ethnicity, NZDep, DHB, month)**
  - **NZ Health Survey controls – 12,000 from 3 years of NZHSs**

Investigators: Michael Baker, Diana Lennon, Jason Gurney, Teuila Percival, Tony Merriman, Nevil Pierse, Debbie Williamson, Nikki Moreland, Colleen Murray, Nigel Wilson, Richard Edwards, Catherine Jackson, Jane Oliver

RF risk factors research

National case-control study methods

Data gathering:

- **Interview with questionnaire.**
- **Blood testing for DNA, immune function markers, vitamin D, ferritin (iron stores).**
- **Throat & nasal swabs for GAS, Staph**
- **Hair sample for nicotine.**
- **Linked records: NHI (previous hospitalisations), Dental records, School size & density, School-based throat-swabbing programme.**

Probiotics

- **Preventing GAS pharyngitis with BLIS-producing oral probiotic**
- **Bacteriocin-Like Inhibitory Substances (BLIS) naturally produced by *Streptococcus salivarius* commensal of the human tongue**
- **John Tagg observed that children colonised with BLIS-producing *S. salivarius* less likely to acquire *S. pyogenes***

Probiotics

Small trial of BLIS K12

- **65 children 3 -12 years with history of recurrent strep infection**
- **Treated daily for 90 days with BLIS K12 (45 children) or control (20), then 6 months non-treatment**
- **Treated children had 90% reduction in strep pharyngitis and 40% in otitis media during treatment.**
- **65% persistence of reduction during 6-month follow-up**
- **Follow-up study using adult subjects reported similar findings**

Source: Di Pierro et al Int. J. Gen. Med. 2012; 5:991-7

Probiotics

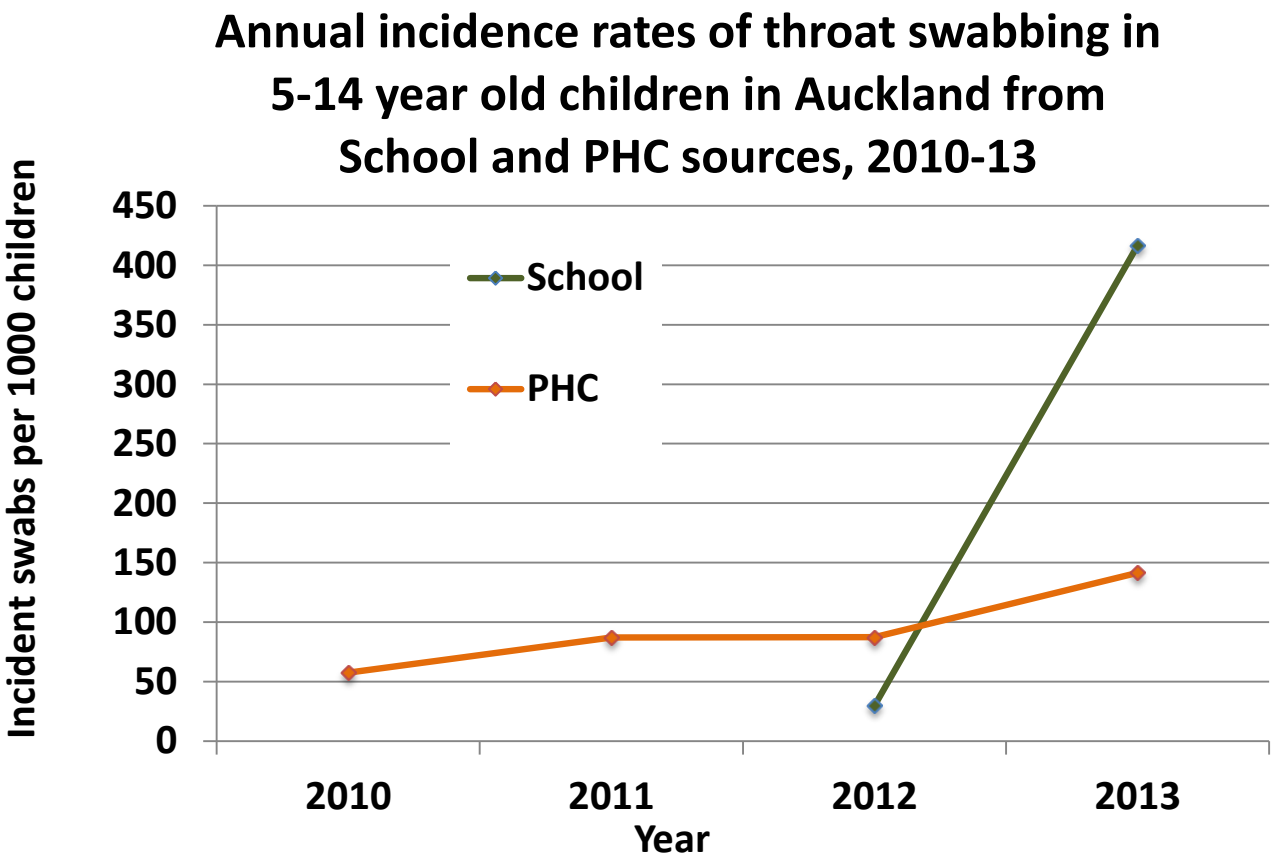
- **Trial – Porirua 2000 children participating in school throat swabbing programme**
- **Randomised to receive BLIS or placebo**
- **Outcome is episodes of detected GAS pharyngitis and carriage of GAS at 12 months**

Investigators: Julian Crane, Michael Baker, Debbie Williamson, Nevil Pierse, Kristin Wickens, Tosh Stanley

Pharyngitis treatment

- **Microbiological culture results of throat swabs performed by Auckland's community laboratory Children 5-14 years, 2010-13 period**
- **161,901 swabs with complete data**
- **Analyses:**
  - **Distribution of swabbing: incidence rates of swabbing, GAS detection and % test positivity (GAS positive swabs/number of swabs). Multivariate analyses in relation to ethnicity**
  - **Linkage to ARF hospitalisations: identified proportion of ARF cases with preceding throat swab (0-63 days pre-admission)**

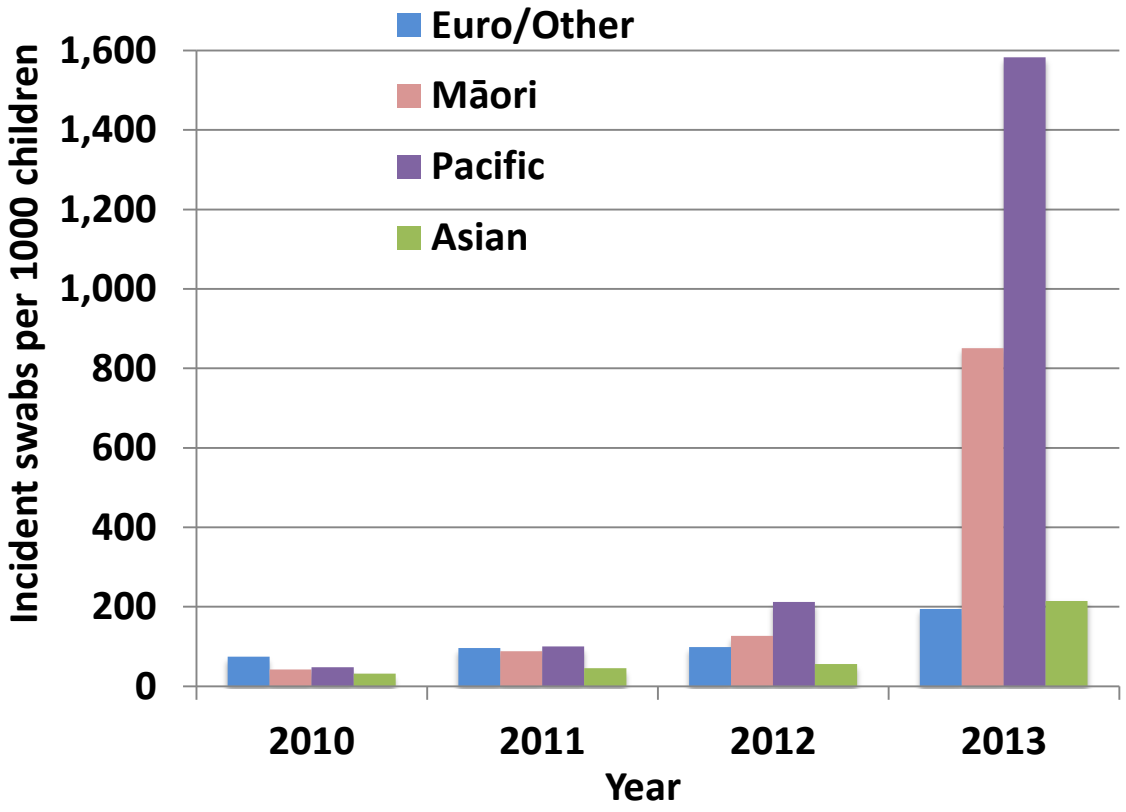
Pharyngitis treatment



Source: Jeffries, Williamson, Baker 2014

Pharyngitis treatment

Ethnic differences in incidence rates of throat swabbing, children 5-14 years, Auckland, 2010-13



Source: Jeffries, Williamson, Baker 2014

Pharyngitis treatment

Year	ARF incidence Auckland region (ADHB, CMDHB and WDHB) 5-14 year olds		Swabbed in preceding 63 days before hospitalisation	
	Number	Rate (/100,000)	Number	Percentage
2010	55	38.4 (30.3, 48.2)	7	9.2 (3.7, 19.0
2011	59			
2012	50			
2013	64	49.1 (39.8, 59.9)	21	21.6 (13.4, 33.1)

Source: Jeffries, Williamson, Baker 2014

GAS Vaccine

- **Trans-Tasman (NZ-Aust) initiative announced in Feb 2013 by Key & Gillard**
- **Initial ~$3m from both governments as part of $30m commitment**
- **3 candidate vaccines**
  - **Combination vaccine (Novartis) - Ready for clinical trials**
  - **30-valent M-protein vaccine (Jim Dale) - Currently in Phase I clinical trials**
  - **J8 peptide from M-protein C-domain (Mike Good) - Currently in Phase I clinical trials**
- **Stated objective:**
  - **Phase 1 trial of candidates that achieve "acceptable coverage of local strains"**
  - **Progression of the strongest candidate to Phase IIb**

GAS Vaccine

Many resource and technical issues

- **Efficacy**
- **Safety**
- **Decision on age group**
- **End points**
- **Location of trials**
- **Funding**
- **Timing**

Source: Moreland, Waddington, Williamson, et al. Vaccine 2014.

GAS Vaccine

- **Superficial infection**
  - **Pharyngitis**
  - **Pyoderma**

- **Invasive diseases**
  - **Septicaemia**
  - **Pneumonia, osteomyelitis…**
  - **Necrotising fasciitis**

- **Toxin mediated diseases**
  - **Scarlet fever**
  - **Streptococcal toxic shock syndrome**

- **Post-streptococcal autoimmune sequelae**
  - **Acute rheumatic fever / rheumatic heart disease**
  - **Post-streptococcal glomerulonephritis**

Easy. High incidence. Protocols available

Easy. High incidence. Protocols available

Possible in Ph III, but v large study, would prob need to have infant and elderly arm. Most likely as large scale effectiveness studies

Not directly. Infer as a result of protection against invasive disease

RHD not possible as Ph III – latent period too long
APSGN fairly localised, limited surveillance, epidemics

Intervention Research

Intervention	Will it work
Improving determinants (income, education, healthcare, housing)	Overwhelming historical evidence in favour, many co-benefits **But** – Takes time, huge resources, political will
Improving specific risk/protective factors (functional crowding, micronutrients)	Good theoretical evidence to reduce household crowding **But** – Poor understanding of pathophysiology of RF, Lack of empirical evidence Risk factors study will provide some data
Probiotic (BLIS) to reduce GAS carriage/pharyngitis	Good theoretical & some empirical evidence **But** – Need to wait for results of trial
Screening & treating GAS pharyngitis (school-based, primary care)	Can prevent some cases Unknown 'herd' effect & positive co-benefits **But** – Limited by coverage & asymptomatic infection, may promote antibiotic resistance
GAS vaccination	Probably the ultimate solution **But** - Vaccine selection & clinical trials uncertain & will take years

Conclusion

- Persistently high rates of RF in Maori & Pacific children not fully unexplained
- Prevention programmes limited by poor knowledge of pathophysiology of RF
- RFPP not associated with decline in RF to date
- Potential interventions within 2-10 years:
  - Probiotic BLIS to reduce GAS pharyngitis
  - Modifiable risk factors identified by national case-control study
  - Possible GAS vaccine trial in NZ/Australia
- Reducing poverty in NZ must remain a major goal for reducing RF & IDs more generally